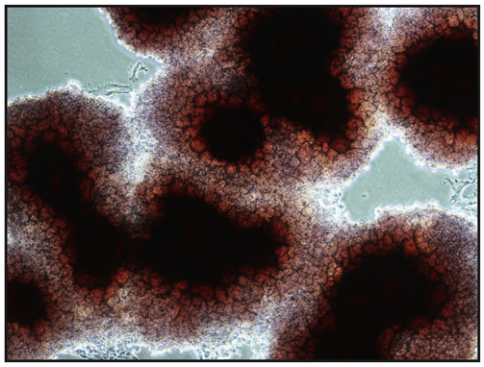
Stem Cell Select

Cell

Lineage commitment requires stem cells to loosen their grip on pluripotency, sequentially picking and choosing among competing genetic programs to realize specific cell fates. New findings described in this issue's Stem Cell Select address the impact of history and cellular memory on differentiation events and reveal critical molecular mediators of stem cell reprogramming and pluripotency.



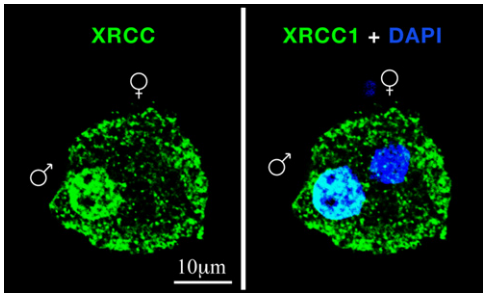
Osteogenic colonies from fibroblast-derived induced pluripotent stem cells stained with alizarin red to detect calcium deposits. Image courtesy of K. Kim.

A Remembrance of Tissues Past

According to two recent reports (Kim et al., 2010; Polo et al., 2010), how you achieve stem cell pluripotency has unexpected consequences. Kim et al. show that reprogrammed pluripotent cells from mice created by somatic cell nuclear transfer differ from those created through the expression of transcription factor cocktails. Their findings suggest that cells reprogrammed by somatic cell nuclear transfer bear greater similarity to embryonic stem cells than induced pluripotent stem (iPS) cells reprogrammed with defined factors, that is, at least prior to extensive passaging. Delving into the molecular basis for this difference reveals that iPS cells retain residual DNA methylation signatures reflecting their cell type of origin. Similar observations are made by Polo et al. in their examination of the gene expression patterns and epigenetic marks of a collection of iPS cells derived from different mouse tissues. The two reports show that iPS cells retain a form of epigenetic memory that makes it possible to identify which tissue iPS cells come from and, more importantly, biases their return to that tissue type upon differentiation. Kim et al. show that further interventions, such as treatment of iPS cells with chromatin-modifying agents or repeating the cycle of differentiation and reprogramming, alter the impact of this epigenetic memory, whereas Polo et al. report that the epigenetic memory is dissipated by continuous passaging of the cells in culture. These findings highlight the notion that pluripotency is not a singular condition but a diverse spectrum of states. They also suggest that a cell's history is not easily erased, bringing to mind the well-known quote from William Faulkner: ''The past is never dead. It's not even past.''

K. Kim et al. (2010). Nature. Published online July 19, 2010. 10.1038/nature09342.
J. M. Polo et al. (2010). Nat. Biotechnol. Published online July 19, 2010. 10.1038/nbt1667.

DNA Repair Gives Germ Cells a Fresh Start



Chromatin-bound XRCC1 (green) in the male pronucleus of the zygote (shown) and in primordial germ cells suggests the presence of single-stranded DNA breaks at the time of DNA demethylation. Image courtesy of P. Hajkova.

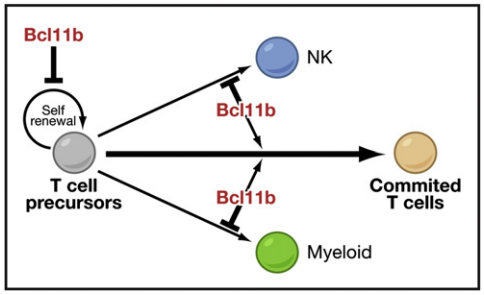
DNA methylation is one of the cell's most stable epigenetic marks. Hajkova et al. (2010) now provide evidence that base excision repair (BER) is actively engaged in the removal of these marks in mouse primordial germ cells (PGCs). On their journey to totipotency, PGCs go through a dramatic transformation in their chromatin landscape, with a major reorganization in their nuclear architecture and changes in histone and DNA modifications. In cells undergoing these reprogramming events, the authors observe an activation of BER pathways, coincident with the removal of methylated cytosines. The activation of BER is also temporally linked to the occurrence of single-stranded DNA (ssDNA) breaks, a step in BER. Consistent with a direct role of BER in DNA demethylation, inhibitors of BER interfere with the removal of methyl-cytosine from the paternal pronucleus of the zygote, another setting in which active DNA demethylation is reported to occur. In relation to the recent papers by Kim et al. (2010) and Polo et al. (2010) discussed above, future work may assess whether promotion of this BER pathway could be used to augment existing methods for the generation of induced pluripotent stem cells.

*P. Hajkova et al. (2010). Science **329**, 78–81.*

A Chronicle of Differentiation Foretold

How do events in embryonic stem cells set the stage for tissue-specific expression later in development? Liber et al. (2010) follow the molecular events at an enhancer specific for pre-B cell differentiation to show how it is primed in embryonic stem cells (ESCs) for activation at a later stage. The core of the pathway uncovered involves a handover between the transcription factor Sox2, which binds the λ5-*VpreB1* enhancer in ESCs, and Sox4, which binds the same region in pro-B cells. In ESCs, Sox2 promotes histone 3 lysine 4 di- and trimethylation, which are activating histone marks, and modulates the recruitment of the Foxd3, a factor that maintains the enhancer and the surrounding regions in a repressed state. At the pro-B cell stage, the Sox and Fox binding sites cooperate (the former with Sox4 bound) to fully activate transcription, thereby enhancing expression of λ5, a protein that acts as a critical surrogate for the immunoglobulin light chain during B cell differentiation. The model proposed by the authors is that factors in ESCs establish active epigenetic marks that then cooperate with tissue-specific factors to drive transcription during differentiation. Future work is likely to address whether ESC factors have a more general role in gene priming in this and other lineage commitment events.

D. Liber et al. (2010). Cell Stem Cell ***7****, 114–126.*



T cell lineage commitment depends on the transcription factor Bcl11b. Image courtesy of L. Li and E.V. Rothenberg.

Holding Back a Natural Killer Instinct

Becoming a T cell from a hematopoietic progenitor means avoiding the temptations of other possibilities along the way, including B cell, macrophage, dendritic cell, and natural killer (NK) cell fates. Three recent papers reveal a transcription factor needed for T cell precursors to take the final step of commitment (Ikawa et al., 2010; Li et al., 2010a; Li et al., 2010b). They show that in the absence of this factor, Bcl11b, would-be T cells can instead be redirected to a natural killer cell fate. NK cells are lymphocytes that directly kill cells recognized as non-self. Li et al. (2010a) demonstrate that Bcl11b is needed both for T lineage commitment and to limit self-renewal, as it promotes the downregulation of both NK cell genes and regulatory genes that are characteristic of stem and progenitor cells. Future work may explore which of the regulated genes are direct targets of Bcl11b. Potential functional consequences of reprogramming T cell progenitors are explored by Li et al. (2010b), who show that even mature T cells can be converted to NK cells by the loss of Bcl11b, and these reprogrammed cells share with native NK cells the capacity to hinder tumor establishment in a mouse model of lung metastasis. The findings of Ikawa et al. may serve as a starting point for efforts to identify the in vivo signals that direct this lineage decision or that maintain progenitors in a multipotent state. They show in culture that an arrest in T cell development can be promoted by interleukin-7 (IL-7), thereby maintaining their myeloid and natural killer cell potential, due to failure to induce Bcl11b. A topic for future examination is to determine how signaling by IL-7 or other cytokines intersects with Bcl11b at the decision point for T cell commitment.

T. Ikawa et al. (2010). Science ***329****, 93–96.*
L. Li et al. (2010a). Science ***329****, 89–93.*
P. Li et al. (2010b). Science ***329****, 85–89.*

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